

BUDGET JUSTIFICATION – CHODERA LABORATORY

Senior/Key Personnel

John D. Chodera, Ph.D., Principal Investigator (2.0 calendar months effort) will serve as PI and Project Director on this project. He is an Assistant Member (Assistant Professor equivalent rank) at the Sloan Kettering Institute---the basic science arm of the Memorial Sloan Kettering Cancer Center---with extensive experience in biomolecular simulation, molecular simulation algorithm development, alchemical free energy calculations for ligand binding, and the use and interpretation of biophysical experiments. He has a publication track record spanning over 15 years of highly regarded work in these fields. He has a decade of experience with the Folding@home worldwide distributed computing project, wrote the GPU-accelerated alchemical free energy calculation code that will be used to compute small molecule binding affinities, has contributed to the development of the GPU-accelerated OpenMM simulation code that will be used for constant-pH simulations, and designed the automated biophysical wetlab that will be used for experimentally measuring binding affinities. He also has extensive experience with computing biophysical observables---including NMR data---from biomolecular simulations. He will manage the overall project and actively supervise the work being performed in this proposal. He will specifically direct the development, implementation, and use of constant-pH algorithms into the OpenMM molecular simulation package and the alchemical free energy computation code. He will also direct the fluorescence binding affinity experiments performed using the automated platform in his laboratory, and coordinate with co-PI Seeliger on other experimental aspects of this project. Together with co-PIs Seeliger and Gunner, he will help design experiments and author publications, and will supervise the training of students and postdocs in his laboratory involved in this project.

Other Personnel

Gregory Ross, D.Phil., Postdoctoral Fellow (3.0 calendar months effort) has extensive experience in biomolecular simulation, free energy calculations, and hybrid Monte Carlo / molecular dynamics algorithm development. Dr.~Ross received his D.Phil.~ from Oxford University, working with Mark Sansom, and worked with Jonathan Essex as a postdoctoral research fellow. Dr.~Ross has particularly relevant expertise for this project, having developed grand canonical Monte Carlo / molecular dynamics methodologies during his work with Jonathan Essex. Dr.~Ross will help develop and implement algorithms for constant-pH molecular dynamics and binding free energy calculations. Effort outside the 5 calendar months of effort budgeted for this project will be spent on other projects and career development activities.

Ari~ Sebastian Rustenburg, Graduate Student in the Weill Cornell Graduate School of Medical Sciences Program in Physiology, Biophysics, and Systems Biology (12.0 calendar months effort) BSc in Pharmaceutical Sciences and an MSc in Drug Discovery and Safety from VU University Amsterdam. Mr. Rustenburg will design, implement, and apply the constant-pH Monte Carlo / molecular dynamics simulation algorithms into OpenMM and YANK (the alchemical free energy code developed by the Chodera lab). Mr. Rustenburg will also carry out the automated pH-dependent binding affinity and isothermal titration calorimetry experiments in the Chodera laboratory.

OTHER DIRECT COSTS

Travel: We ask for \$3,000/year in travel support to allow the PI and either PhD student or postdoc to attend one national meeting each year to present their progress and results on this project.

Publication fees: We request \$2,500/year to defer publication fees.

Materials and Supplies: We request \$15,000/year for experimental laboratory supplies and instrument usage fees to cover the costs of engineering protein mutants, performing fluorescence binding assays, and executing calorimetry experiments to dissect the contribution of protonation state changes to binding affinities.